Journal of Neurology (2019) 266:398–410
https://doi.org/10.1007/s00415-018-9143-x

ORIGINAL COMMUNICATION

Motor neuron involvement in anti-Ma2-associated paraneoplastic neurological syndrome

Alberto Vogrig[1,2,3,4] · Bastien Joubert[1,2,3] · Aurélien Maureille[1,2,3,5] · Laure Thomas[1,2,3] · Emilien Bernard[6] · Nathalie Streichenberger[7] · Francois Cotton[8,9] · Francois Ducray[1,2,3] · Jérome Honnorat[1,2,3,10]

Received: 1 October 2018 / Revised: 12 November 2018 / Accepted: 26 November 2018 / Published online: 29 November 2018

Abstract

Objective To present clinical, radiological, and pathological features of a cohort of patients with motor neuron involvement in association with anti-Ma2 antibodies (Ma2-Ab).

Methods Retrospective case-series of patients with definite paraneoplastic neurological syndrome (PNS) and Ma2-Ab, and cases identified from a review of the literature.

Results Among 33 Ma2-Ab patients referred between 2002 and 2016, we retrospectively identified three patients (9.1%) with a motor neuron syndrome (MNS). Seven additional cases were retrieved among the 75 Ma2-patients reported in the literature (9.3%). A total of ten patients are, therefore, described herein. MNS was evident as combined upper and lower MNS in four patients, isolated upper MNS in two, and isolated lower MNS in one; three patients were diagnosed with myeloradiculopathy. The most common MNS signs/symptoms were: hyperreflexia (80%), proximal weakness (60%), proximal upper-limb fasciculations (50%), head drop (40%), and dysarthria/dysphagia (30%). Brain MRI abnormalities included bilateral pyramidal tract T2-weighted/FLAIR hyperintensities (three patients). Spine MRI found bilateral, symmetric, T2-weighted signal abnormalities in the anterior horn in two patients. CSF examination was abnormal in nine patients. Cancer was found in seven patients (four testicular, two lung, and one mesothelioma). Eight patients underwent first-line immunotherapy. Second-line immunotherapy was adopted in all our patients and in none of those identified in the literature. Motor improvement was observed in 33% of our patients, and 20% in the literature series.

Conclusions Motor neuron involvement could complicate Ma2-Ab-associated PNS in almost 10% of patients and must be carefully studied to adapt treatment. This disorder differs from amyotrophic lateral sclerosis.

Keywords Paraneoplastic syndromes · Motor neuron syndrome · Amyotrophic lateral sclerosis · Anti-Ma · Myelopathy · Radiculopathy

✉ Jérome Honnorat
jerome.honnorat@chu-lyon.fr

[1] French Reference Center of Paraneoplastic Neurological Syndrome, Hospices Civils de Lyon, Hôpital Neurologique, Lyon, France

[2] SynatAc Team, NeuroMyoGene Institute, INSERM U1217/CNRS UMR5310, Lyon, France

[3] University Claude Bernard Lyon 1, Université de Lyon, Lyon, France

[4] Department of Neurosciences, Santa Maria della Misericordia University Hospital, Udine, Italy

[5] Department of Neurology, Lille University Hospital, Lille, France

[6] Department of Electroneuromyography and Neuromuscular Diseases, Hospices Civils de Lyon, Lyon, France

[7] Centre de Neuropathologie Est, Hospices Civils de Lyon, Université Claude Bernard Lyon1, Institut NeuroMyogène, CNRS UMR 5310, INSERM U1217, Lyon, France

[8] Service de Radiologie, Centre Hospitalier Lyon-Sud, Hospices Civils de Lyon, Pierre-Bénite, France

[9] CREATIS-CNRS UMR 5220 & INSERM U1044, University Claude Bernard Lyon 1, Lyon, France

[10] Centre de Référence National pour les Syndromes Neurologiques Paranéoplasique, Hôpital Neurologique, 59 Boulevard Pinel, 69677 Bron Cedex, France

Introduction

Paraneoplastic neurological syndromes (PNS) are a heterogeneous group of disorders with a presumed immune-mediated pathogenesis that develop in 1 in every 10,000 patients with cancer [1]. Exceptionally (2% of all PNS cases), a syndrome characterized by prominent upper and/or lower motor neuron dysfunction (at times resembling sporadic amyotrophic lateral sclerosis, ALS) ensues in patients with neoplasia and detectable onconeural antibodies (Ab) [2]. However, its prevalence is so low that it is not clear in the literature whether a paraneoplastic motor neuron syndrome (MNS) really exists, or just reflects the effect of chance (combined occurrence of sporadic ALS and PNS) [3]. Using the available diagnostic criteria for PNS, the presence of well-characterized Ab (including anti-Hu, Yo, CV2/CRMP5, Ri, Ma2, and amphiphysin), even with an atypical syndrome (e.g. MNS), permits the diagnosis of "definite PNS" [4]. Anti-Ma2 antibodies (Ma2-Ab) were originally described in men with testicular cancer with clinical and radiological involvement of limbic structures, diencephalon, or brainstem [5]. After the identification of a patient with MNS in conjunction with Ma2-Ab we carefully reviewed all our cases as well as the literature and herein describe these patients.

Methods

After the identification of a patient with Ma2-Ab and MNS, we retrospectively reviewed the medical and radiological records of all patients who were referred to the French national reference center for paraneoplastic neurological diseases between January 1, 2002, and December 31, 2016 for suspected PNS (possible or definite, using Graus criteria [4]) and who received a definite diagnosis of Ma2-Ab-associated PNS based on Ab-positivity in serum and/or cerebrospinal fluid (CSF). All patients underwent a comprehensive laboratory examination for suspected PNS, including both immunohistochemistry on rat brain sections and dot-blot analysis on recombinant proteins (Euroimmun, Lubeck, Germany and RAVO Diagnostika, Freiburg, Germany) for the presence of onconeuronal Abs (anti-Hu, Yo, CV2/CRMP5, Ri, Ma2, and amphiphysin). All patients were also tested for the presence of an underlying tumor, using whole-body computed tomography (CT), ^{18}Fluorodeoxyglucose (^{18}F-FDG) positron emission tomography/CT, and testicular ultrasound in male patients (given the strong association with testicular cancer). Demographic, clinical, radiological, and neurophysiological data of all the patients were reviewed for further analysis. The inclusion criteria for the present study were as follows: (1) presence, over the course of the disease, of clinical findings consistent with upper motor neuron dysfunction [e.g. weakness, spasticity, pathological hyperreflexia (including Babinski sign), pseudobulbar (spastic bulbar) palsy]; (2) clinical findings consistent with lower motor neuron dysfunction (e.g. weakness, muscle atrophy, hyporeflexia, fasciculations); (3) neurophysiological findings showing evidence of lower motor neuron dysfunction (neurogenic potentials, fibrillation potentials and/or sharp waves). Electrophysiological evidence of upper motor neuron dysfunction (i.e. an abnormal central motor conduction time, mostly prolonged, together with prolonged motor evoked potentials latencies) were considered as supportive findings only in the presence of clinical evidence of a pyramidal syndrome. The main exclusion criterion was the presence of alternative disease (other than PNS) as the cause of the above-mentioned abnormalities on clinical examination. Careful examination of brain and spinal cord magnetic resonance imaging (MRI) of the selected patients was done by a neuroradiologist with 20 years' experience (FC). MNS involvement was described in detail using the following classification: MNS involving both upper and lower motor neurons; pure upper MNS; pure lower MNS; myeloradiculopathy (when a combination of myelopathy and [poly]-radiculopathy was suggested by neurological examination). Previously reported (January 1970 to January 2018) cases of anti-Ma2 syndrome with MNS-like presentation were identified via PubMed searches using the terms "paraneoplastic", "anti-Ma2", "motor neuron" and "amyotrophic lateral sclerosis". We retrieved all relevant articles and checked additional references cited in these.

The presence of a concomitant "classical" or "non-classical" neurological syndrome was further specified in all the patients according to the Graus criteria [4].

Written consent was obtained from all patients with the approval of the Institutional Review Board of the University Claude Bernard Lyon 1 and Hospices Civils de Lyon.

Results

Clinical findings and tumor associations in the present Ma2-Ab cohort

During the study period (2002–2016), 33 patients initially referred to the national reference center for a diagnosis of suspected PNS had clear Ma2-Ab positivity on serum and/or CSF sample. Detailed information regarding demographical data, neurological syndrome, clinical evolution, and oncological associations was available for 31 of them. Twenty-three (74%) were male; median age was 55 years

(range 25–86). Cancer was discovered in 21 (68%) and included testicular cancer in 10, lung cancer in 6, and gastrointestinal cancer in 2. Less common tumors were found in three patients (oral cancer, pleural mesothelioma, and non-Hodgkin lymphoma). Patients with Ma2-Ab syndrome in the context of testicular cancer trend to be younger (median age: 41 years). Overall, neurological involvement at presentation included: limbic encephalitis in 13 patients (32% of sites involved), brainstem encephalitis in 10 (24%), cerebellar syndrome in 9 (22%), diencephalic encephalitis in 4 (10%), opsoclonus-myoclonus in 2 (5%), polyneuropathy in 2 (5%), and polyradiculopathy in 1 (2%; Fig. 1). Ten patients presented with multiple neurological site involvement (three had concomitant limbic and brainstem involvement, three cerebellar and brainstem involvement, two concurrent opsoclonus-myoclonus and cerebellar syndrome, one limbic and diencephalic involvement, and one limbic encephalitis and cerebellar syndrome).

Anti-Ma2-associated MNS

There were 3 (9.1%) Ma2-Ab patients who had an MNS during the course of their illness (Table 1) and are described in detail below.

Patient 1

The index case was a 59-year-old man who presented initially with narcolepsy–cataplexy (NC), hyperphagia, and sexual dysfunction. His neurological picture progressed gradually, and 18 months after initial presentation was evaluated for the subacute worsening of gait and appearance

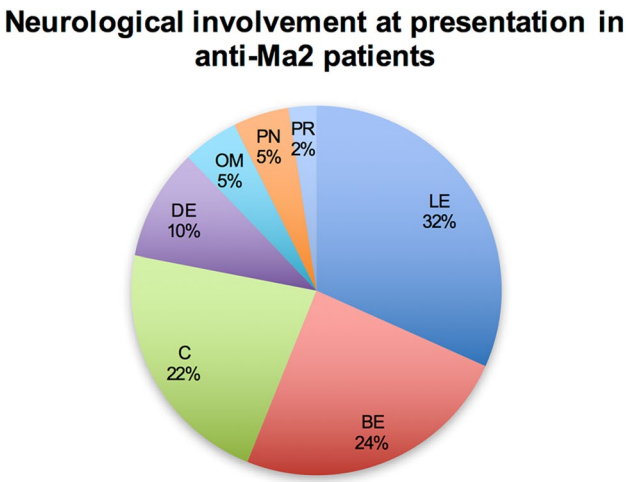

Fig. 1 Neurological involvement at presentation in Ma2-Ab patients. *LE* limbic encephalitis, *BE* brainstem encephalitis, *C* cerebellar syndrome, *DE* diencephalic encephalitis, *OM* opsoclonus–myoclonus, *PN* polyneuropathy, *PR* polyradiculopathy

of bulbar symptoms (dysarthria and dysphagia). Neurological examination found diffuse hyperactive reflexes and axial rigidity. Brain MRI demonstrated FLAIR hypersignal involving the cortico-spinal tract (CST; Fig. 2a–d). Spine MRI found slight C4-D1 hypersignal involving mainly the anterior column. CSF examination found signs of inflammation [7 lymphocytes per cubic millimeter; normal protein content; and positive oligoclonal bands (OCBs)]. Ma2-Ab were detected in the serum and the CSF. No associated tumor was found despite comprehensive screening, including testicular ultrasound. The patient was treated with corticosteroid bolus and bilateral orchiectomy, given the strong association known with this Ab-positivity and occult testicular cancer, but no cancer was found. Despite all these measures, no clear improvement was noticed at follow-up examinations. Aggressive, second-line, treatment with cyclophosphamide (monthly intravenous infusions) was started and resulted in the resolution of sleep disturbances and evident improvement of gait.

Patient 2

After this initial observation, we noticed a second patient, a 56-year-old man, who presented initially very similarly to the index case. In particular, NC and sexual dysfunction were the initial complaints, followed 19 months later by gait disturbances and severe dysphagia. In this second case, neurological examination found signs consistent with lower motor neuron dysfunction (diffuse hypoactive reflexes, proximal weakness with atrophy and fasciculations). Electromyography (EMG) confirmed severe axonal motor damage and neurogenic pattern with active denervation (cervical muscles and trapezius, bilaterally). Brain MRI found FLAIR hypersignal involving the CST (Fig. 2e–h). CSF examination found modestly increased protein content and positive OCBs. Ma2-Ab were detected in the serum and the CSF. A germ cell tumor was found (positive retroperitoneal lymph node, in the context of possible "burn-out seminoma") and the patient was treated with orchiectomy and corticosteroid bolus, without clear effect on clinical symptoms. Second-line therapy with cyclophosphamide (12 monthly intravenous infusions) was adopted and resulted in the stabilization of motor symptoms and initial improvement of sleep disturbances, without any concurrent change in narcolepsy treatment (sodium oxybate). The adjunct of rituximab did not result in further improvement.

Patient 3

The third patient was a 47-year-old man who was diagnosed with testicular germ cell tumor for 1 year. He was treated with adjuvant chemotherapy (including bleomycin, etoposide, and cisplatin) and bilateral orchiectomy, and was stable

Table 1 Characteristics of patients with Ma2-Ab paraneoplastic syndrome and motor neuron syndrome

Pt N°	Sex/age (year)	References	Initial symptoms	Interval from initial symptoms to first sign of MNS	Signs of UMN or LMN dysfunctions	Brain MRI	Spine MRI	EMG/MEP/SEP	CSF (cells/protein/OCB)	Tumor	Treatments and outcome
1	M/59	Present series	Narcolepsy–Cataplexy Hyperphagia Sexual dysfunction	18 months	Diffuse hyperreflexia Axial rigidity Dysarthria Dysphagia	FLAIR hypersignal involving CST and cerebellar peduncles	Slight T2 hypersignal C4-D1	EMG: normal findings	Abnormal (7/mm^3; 27 mg/dl/OCB+)	Not found	Corticosteroids, cyclophosphamide Bilateral orchiectomy Resolution of sleep disturbances; improvement of gait
2	M/56	Present series	Narcolepsy–Cataplexy sexual dysfunction	19 months	Diffuse hyporeflexia Proximal quadriparesis Amyotrophy Fasciculations Severe dysphagia	FLAIR hypersignal involving CST	Normal	EMG:severe axonal motor damage, active denervation (cervical muscles and trapezius, bilaterally)	Abnormal (4/mm^3; 63 mg/dl/OCB+)	Germ cell tumor (positive retroperitoneal lymph node, in the context of possible burn-out seminoma)	Corticosteroids, cyclophosphamide, rituximab Bilateral orchiectomy Improvement of sleep disturbances
3	M/47	Present series	Memory deficits Behavioral abnormalities Vertical gaze palsy	6 months	Diffuse hyperreflexia Shoulder girdle paresis amyotrophy Head-drop Dysphagia	Bilateral FLAIR MTL hypersignalfollowed later by CST hypersignal	Symmetric tract-specific T2 hyperintesity	EMG: severe axonal motor damage, active denervation (cervical muscles)	Abnormal (0/mm^3; 46 mg/dl/OCB+)	Testicular germ cell tumor	IVIG, Corticosteroids, rituximab, cyclophosphamide Bilateral orchiectomy Stabilization of symptoms
4	M/58	Dalmau et al. [5]	Shoulder pain, segmental hypoesthesia	Monophasic	Proximal weakness of the upper extremities Absent biceps and brachioradialis reflexes Muscle atrophy Fasciculations	Normal	Normal	N.A	Abnormal (pleocytosis; elevated protein concentration/OCB+)	Lung adenocarcinoma	Tx N.A The patient died 5 months after initial presentation

Table 1 (continued)

Pt N°	Sex/age (year)	References	Initial symptoms	Interval from initial symptoms to first sign of MNS	Signs of UMN or LMN dysfunctions	Brain MRI	Spine MRI	EMG/MEP/SEP	CSF (cells/protein/OCB)	Tumor	Treatments and outcome
5	M/36	Waragai et al. [6]	Progressive amnesia, hypersomnia diplopia, and generalized seizures	8 months	Progressive muscular atrophy Weakness, and fasciculations of the upper extremities, shoulder girdle, and neck Later, head drop ensued Bilateral Babinski's sign	FLAIR hypersignal involving bilateral MTL, R frontal cortex and R insula	Symmetric tract-specific T2 hyperintesity	EMG: neurogenic changes in the muscles of the upper extremities and shoulder girdle, including paraspinal muscles Normal MEP and SEP	Abnormal (5/mm^3; 83 mg/dl/ OCB N.A.)	Testicular germ cell tumor	IVIG, Corticosteroids Bilateral orchiectomy Stabilization of symptoms
6	M/70	Hoffmann et al. [7]	Gait difficulties	Monophasic	UMN + LMN syndrome (details N.A.)	N.A	N.A	N.A	Abnormal (0/mm^3; 52 mg/dl/ OCB N.A.)	Not found	None Stable at follow-up
7	F/50	Piccolo et al. [8]	Leg stiffness	Monophasic	Muscle rigidity of lower limbs, brisk deep tendon reflexes Severe spastic gait	Normal	Normal	No signs of LMN involvement. Electrophysiological evidence of UMN hyperexcitability	Abnormal (N.A./N.A./OCB+)	Not found	Corticosteroids Initial improvement, followed by rapid worsening after corticosteroid withdrawal Stable after a 4-year follow-up

Table 1 (continued)

Pt N°	Sex/age (year)	References	Initial symptoms	Interval from initial symptoms to first sign of MNS	Signs of UMN or LMN dysfunctions	Brain MRI	Spine MRI	EMG/MEP/SEP	CSF (cells/protein/OCB)	Tumor	Treatments and outcome
8	M/46	Murphy et al. [9]	Left hand weakness, abnormal "spreading out sensation"	Monophasic	Head drop Wasting of both forearms and intrinsic hand muscles Fasciculations Asymmetric, proximal and distal weakness of both arms Reflexes were brisk in the upper limbs	Normal	Normal	Neurophysiology of the upper limbs demonstrated reduced motor amplitudes and acute and chronic denervation but no conduction block	Abnormal (normal/normal/OCB+)	Testicular seminoma	IVIG, Corticosteroids, PLEX Bilateral orchidectomy Stabilization (1-year follow-up)
9	M/68	Geeva-singa et al. [10]	Progressive dysphagia and dysarthria, associated with behavior abnormalities and memory deficits	Monophasic	Bulbar dysfunction Tongue wasting Fasciculations Dysarthria Mild neck flexion weakness and a 'split hand' pattern of wasting	Severe bifrontal atrophy	N.A	Widespread ongoing (fibrillation potentials and positive sharp waves) and chronic denervation changes in multiple (cranial cervical, thoracic and lumbosacral) segments consistent with the diagnosis of MNS Normal SEP	Normal (OCB−)	Lung adenocarcinoma	PLEX Worsening of lower limb weakness and development of orthopnoea

Table 1 (continued)

Pt N°	Sex/age (year)	References	Initial symptoms	Interval from initial symptoms to first sign of MNS	Signs of UMN or LMN dysfunctions	Brain MRI	Spine MRI	EMG/MEP/SEP	CSF (cells/protein/OCB)	Tumor	Treatments and outcome
10	M/58	Vogrig et al. [11]	Temporal lobe seizures	15 days	Paraparesis, Brisk knee jerks, and proximal lower limb muscle atrophy, No sensory abnormalities	T2-weighted hyperintensity with contrast enhancement in the L MTL	Gad Enhancement of nerve roots	Proximal and distal axonal involvement at lower limbs with denervation, in addition to central alteration of MEP	Abnormal (6/mm^3; 53 mg/dl; OCB +)	Pleural mesothelioma	Corticosteroids, IVIG Cancer CTX Stabilization

CSF cerebrospinal fluid, *CST* corticospinal tract, *CTX* chemotherapy, *EMG* electromyography, *F* female, *FLAIR* fluid-attenuated inversion recovery, *IVIG* intravenous immunoglobulin, *L* left, *LMN* lower motor neuron, *M* male, *MEP* motor evoked potentials, *MNS* motor neuron syndrome, *MRI* magnetic resonance imaging, *MTL* mesial temporal lobe, *N.A.* not available/not performed, *OCB* oligoclonal band(s), *PLEX* plasmapheresis, *Pt* patient, *R* right, *SEP* sensory evoked potentials, *UMN* upper motor neuron, *y* years

at follow-up. In 2016, he was evaluated in another hospital for aboulia, apathy, and psychomotor slowing. Initially, a diagnosis of major depressive episode was made. Later, memory disturbances ensued (mini-mental state examination score: 22/30) together with vertical gaze palsy. He was, therefore, admitted to our department where he underwent brain MRI (bilateral mesial temporal lobe FLAIR hyperintensity). Ma2-Ab were detected in the serum. The patient was treated with corticosteroid bolus and intravenous immunoglobulin. Six months after initial presentation, at a follow-up examination, the appearance of a MNS involving both upper and lower motor neurons was observed. In particular, the patient exhibited head-drop, dysphagia, proximal upper limbs muscle deficits, and atrophy of the shoulder girdle; diffuse hyperactive reflexes were also noticed. A follow-up brain MRI showed hypersignal involving the CST (Fig. 2i). Spine MRI found symmetric, tract-specific, T2-hyperintensity involving the anterior column (Fig. 2j, k). CSF examination found positive OCBs. Given the EMG findings of severe axonal damage and neurogenic pattern with active denervation, a muscle biopsy was performed and was consistent with acute denervation atrophy, while excluding myositis (Fig. 3a–d). A diagnosis of Ma2-Ab associated MNS was made and the patient was treated with cyclophosphamide and rituximab combination, which resulted in stabilization of the clinical symptoms.

Review of the literature

To assess the relevance of our findings, we searched for similar presentations in the literature, retrieving seven additional cases [5–11] among a total of 75 reported patients with Ma2-Ab paraneoplastic neurological syndrome [5–29] (9.3%). By combining our cases with those described in the literature, we were able to define the clinical phenotype of Ma2-Ab-associated MNS. All the cases are presented in Table 1.

Among all cases ($n=10$), 9 (90%) were male and median age was 57 years. Half of the patients ($n=5$) exhibited MNS-like features at disease onset (monophasic disease group), whereas the remaining half initially showed symptoms indicative of limbic/diencephalic involvement (mainly hypersomnia, three cases), followed later by overt MNS (biphasic disease group). The median interval between the first and the second syndrome was 8 months (range 0.5–19 months). MNS was evident as motor neuron disease involving both upper and lower motor neurons in four patients, pure upper MNS in two patients, and pure lower MNS in 1; three patients were diagnosed as having a myeloradiculopathy. In the latter group, the patients demonstrated signs and symptoms of motor neuron involvement as well, and MRI of the brain and spine did not show any concomitant compressive/structural abnormality.

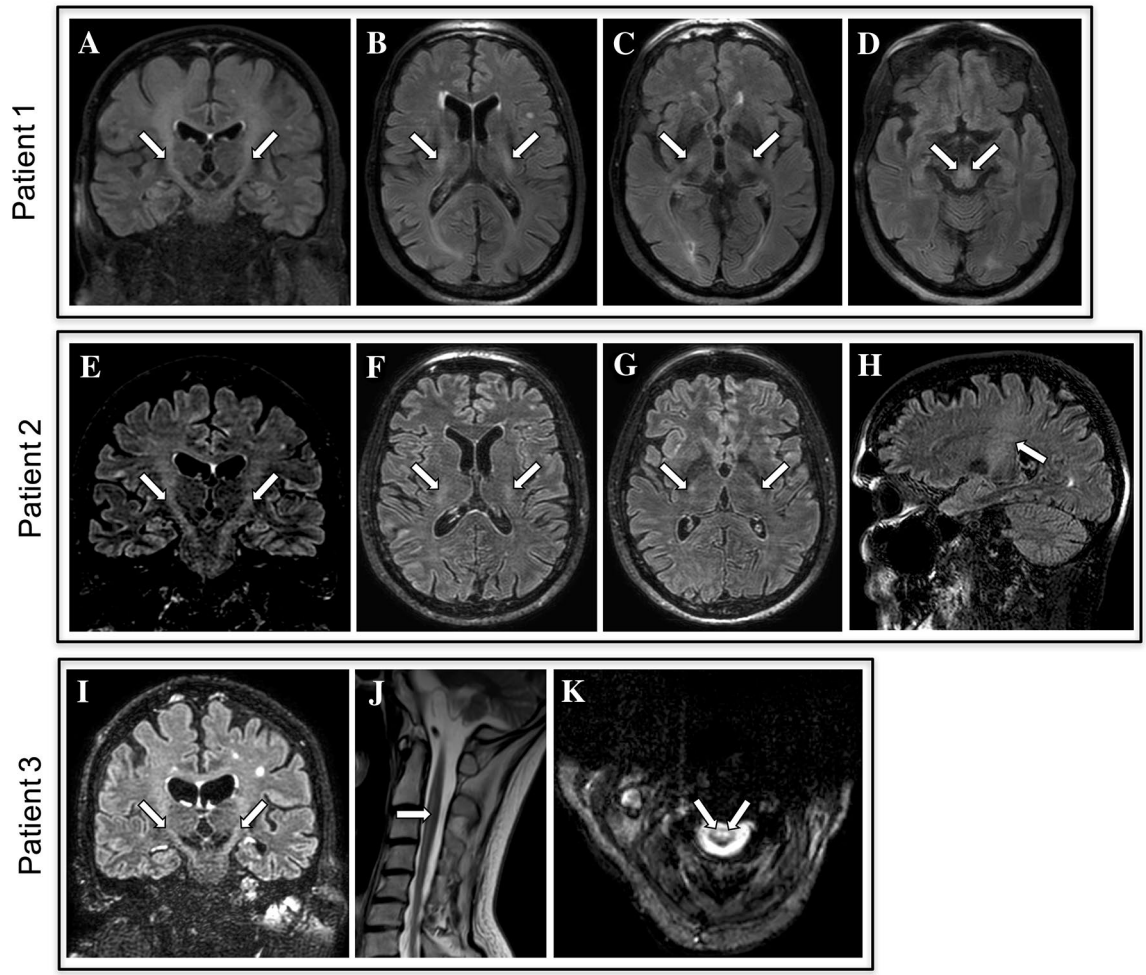

Fig. 2 Magnetic resonance imaging (MRI) findings in Ma2-Ab-associated motor neuron syndrome. Brain MRI from patients 1–3 are presented. Hypersignal (arrows) involving the corticospinal tract (CST) is evident in coronal (**a, e, i**), axial (**b–d, f, g**) and sagittal (**h**) Fluid Attenuated Inversion Recovery (FLAIR) sections. CST hyperintensity (arrows) is also found in the cervical spinal cord of Patient 3 (J: sagittal T2-weighted and K: axial gradient echo T2-weighted spine MRI)

The most common MNS signs/symptoms were: regional or diffuse hyperreflexia (eight patients, 80%), proximal weakness (six patients, 60%), proximal upper-limb fasciculations (five patients, 50%), head drop (four patients, 40%), dysarthria/dysphagia (three patients, 30%). The presence of proximal weakness led first to the exclusion of a concomitant (presumably corticosteroid-induced) myopathy using EMG, creatine kinase (CK) test, and muscle biopsy (one patient); none of these studies was in favor of a primary muscular disease. Brain MRI was performed in nine patients and was abnormal in six of them (67%). MRI abnormalities included mesial temporal lobe (hippocampus and/or amygdala) FLAIR hyperintensities (three patients), or bilateral pyramidal tract T2-weighted or FLAIR hyperintensities (three cases; Fig. 2), and cerebral atrophy (especially for Patient 3 of our series). Bilateral hyperintensities along the large myelinated pyramidal tract fibers was observed from the centrum semi-ovale to the crus cerebri bilaterally, giving a classic "wine glass" appearance on coronal sections. The precentral gyrus seemed to be spared. Spine (mainly cervical) MRI was performed in eight patients and was abnormal in four (two of them with bilateral and symmetric T2-weighted, tract-specific, signal abnormalities in the anterior horn). Detailed information regarding EMG examination was available for eight patients; 6 (75%) showed ongoing denervation changes, and none showed myopathic EMG changes (see Table 1 for further details). CSF examination was abnormal in nine patients (90%); the most common abnormality was the presence of CSF-exclusive OCBs (present in seven out of eight patients tested). CSF leukocyte count was either normal (seven patients), or mildly elevated (three patients). Protein content was normal in four cases and modestly elevated in six, respectively. A comprehensive tumor screening was undertaken in all patients, and revealed

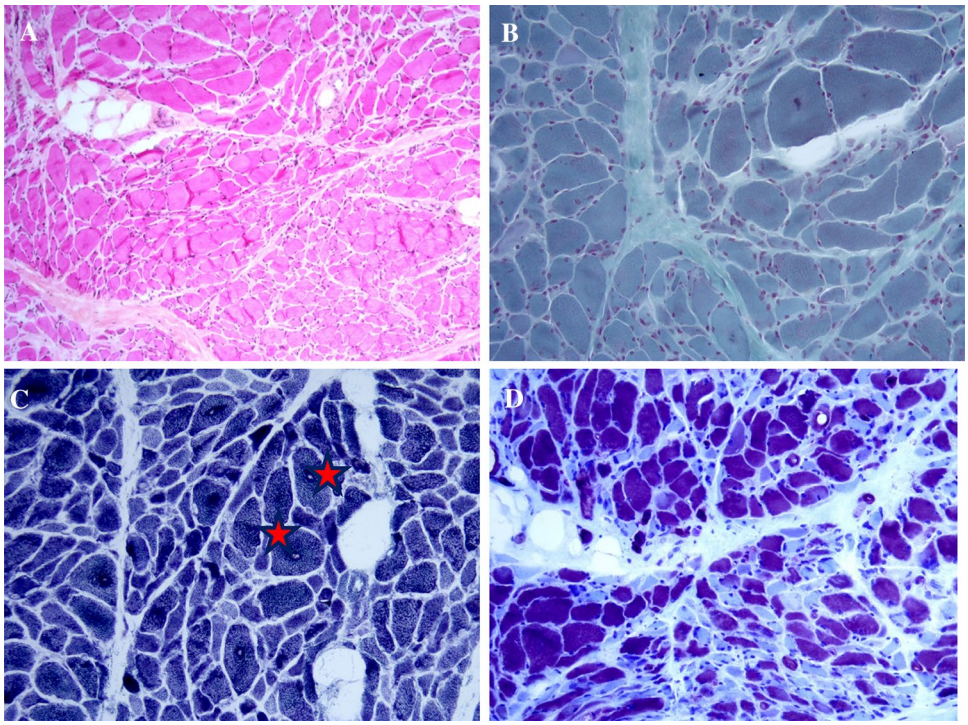

Fig. 3 Pathologic findings in muscle biopsy from Patient 3. **A** HPS ×10: Atrophic and hypertrophic fibers are observed with rare nuclear internalizations within fibrotic and adipose interstitial tissue. **b** Modified trichrome stain ×20 showing the same morphological features with few central inclusions within hypertrophic fibers. **c** DPNH ×20: numerous target fibers reflecting acute denervation process (red stars). **d** ATP 4.35 × 20: predominance of type II atrophic fibers mixed with atrophic and hypertrophic type I fibers. No real fiber type grouping is evident in this acute denervation process

the presence of cancer in 7 (70%): four testicular tumors, two lung tumors, and one pleural mesothelioma. All patients with clinico-radiological evidence of testicular mass and one patient without this evidence (but with strong Ma2-Ab positivity) underwent bilateral orchiectomy; in the latter case no tumor cells were found. A total of eight patients (80%) underwent immunotherapy. First-line immunotherapy consisted of corticosteroids in seven cases, intravenous immunoglobulin in four, and plasmapheresis in two. Second-line immunotherapy was adopted in all patients in our series (with either cyclophosphamide, rituximab, or their combination; see Table 1) and in none of the patients reported in the literature. Immunotherapy resulted in clinically relevant improvement of MNS in one out of three patients in our series (33%), and one out of five patients in those identified in the literature (20%). Remarkably, among all identified cases, only one patient rapidly progressed despite treatment, while the others showed at least temporary stabilization of symptoms. Resolution of sleep disturbances after immunotherapy was noticed in two patients that presented initially with prominent diencephalic involvement. Usually, MNS was more refractory to immunotherapy, but two patients with a pure upper MNS (Patient 1, from our series, and Patient 4, from the literature) showed a clear beneficial effect

Table 2 Diagnostic classification of the patients using the Graus criteria [4]

Pt N°	Neurological syndrome	Features consistent with "typical" Ma2-PNS [5]	Tumor	Well-characterized Onconeural Abs	Final PNS Classification
1	Non-classical	Diencephalic involvement	–	Ma2	Definite
2	Non-classical	Diencephalic involvement	+	Ma2	Definite
3	Classical	Limbic involvement	+	Ma2	Definite
4	Classical	–	+	Ma2	Definite
5	Classical	Limbic involvement	+	Ma2	Definite
6	Non-classical	N.A	–	Ma2	Definite
7	Non-classical	–	–	Ma2	Definite
8	Non-classical	–	+	Ma2	Definite
9	Classical	Limbic involvement	+	Ma2	Definite
10	Classical	Limbic involvement	+	Ma2	Definite

Abs antibodies, *PNS* paraneoplastic neurological syndrome, *Pt* patient

on motor symptoms. Patient 4 had later a relapse following corticosteroid discontinuation.

We reviewed the ten patients with Ma2 Abs and MNS to classify them according to the Graus criteria [4] (Table 2). Half of them (5) had a concomitant "classical PNS", whereas the others manifested a "non-classical PNS". Interestingly, all the patients without cancer manifested a "non-classical" syndrome (Patient 1, 6 and 7). Despite having a "non-classical syndrome", Patient 1 manifested a "typical" anti-Ma2 diencephalic involvement. Given the presence of Ma2 Abs, all the participants of the present study (10) received a final diagnosis of "definite PNS" according to the international criteria.

Discussion

This is, to the best of our knowledge, the first study to examine the prevalence and clinical features of Ma2-Ab-associated paraneoplastic MNS. The series includes all patients referred to the French national reference center over 15 years, and is the second largest Ma2-Ab series published to date [5]. By combining our cases and those reported in the literature, we demonstrate that Ma2-Ab patients can develop over the course of their illness a MNS in almost 10% of cases, with various combinations of upper and/or lower motor neuron signs and symptoms. With all these patients, we were able to define the phenotypic spectrum of MNS in the context of Ma2-Ab autoimmunity. In agreement with previous observations [5] most of the patients with Ma2-Ab were male, middle-aged adults, with associated cancer, usually a testicular germ cell tumor or a lung cancer. Half of them developed MNS as first neurological manifestation, whereas the other half showed a two-step disease course, with initial limbic/diencephalic involvement, followed months later by motor neuron disease or myeloradiculopathy. Interestingly, among the patients seen in our center, 2/33 presented initially with clinically and polysomnography-proven NC. In the literature, only five cases of Ma2-associated narcolepsy have been described, together with the detection of low hypocretin-1 CSF concentration [30, 31]. In addition to its rarity, we were surprised by the finding that both our NC patients developed subsequently an MNS, following a strikingly similar evolution. Moreover, the third patient that did not have a clear NC diagnosis, referred to our center for paraneoplastic Ma2-Ab limbic and brainstem encephalitis, exhibited "severe prostration" during his first hospital stay according to the available medical records. We, therefore, hypothesize that excessive daytime sleepiness was also present in Patient 3. The motor neuron involvement in Ma2-Ab syndrome was variable among the ten cases identified, and included a combination of upper and lower motor neuron signs/symptoms, a pure upper MNS, or isolated lower MNS. Clinically diagnosed myeloradiculopathy, without MRI or laboratory evidence of alternative (structural/compressive, vascular, or infectious) etiologies, was detected in three patients. Overall, the most common neurological complaint was proximal weakness, at times resembling a primary muscle disease. Considering that most of the patients have been already treated with corticosteroids at the time of proximal weakness onset, corticosteroid-induced myopathy was considered in the differential diagnosis. Later in the course of the disease, regional or diffuse hyperreflexia became apparent in the majority of patients, making this possibility unlikely. Symptoms/signs indicative of bulbar (dysarthria/dysphagia) or cervical (head drop) weakness were also common. Neuroimaging studies often found focal abnormalities involving the limbic structures, and/or CST alterations, at both supra- and infra-tentorial level, including cervical cord tract-specific abnormalities (anterior horn column). The latter are known to be common findings in isolated paraneoplastic myelopathy [32] but bilateral brain CST hyperintensity—believed to be more specific for ALS—was never reported in association with paraneoplastic syndromes. Healthy subjects can also express slight CST hyperintensity on brain MRI (especially 3T MRI), but usually this finding is restricted to T2-weighted sequences only; it is not as marked as in the cases described herein, and does not associate with cervical cord CST alterations [33]. Bilateral involvement of the CST has also been reported in inflammatory conditions such as neuromyelitis optica spectrum disorder (NMOSD) [34]; genetic diseases such as the X-linked form of Charcot–Marie–Tooth disease (CMT1X) [35]; leukodystrophy such as leukoencephalopathy with brain stem and spinal cord involvement and lactate elevation (LBSL) [36], hypomyelination with brainstem and spinal cord involvement and leg spasticity (HBSL) [37], and adrenoleukodystrophy [38]; infectious conditions (HSV, HTLV1) [39, 40]; and toxicity due to chemotherapy such as capecitabine [41] (the latter drug was not used in our patients). In LBSL, there is a selective involvement of the pyramidal tracts through their entire length, including the spinal cord [36]. In NMOSD, involvement of the CST, either unilateral or bilateral, is a typical brain lesion pattern and a new criterion in the recently revised diagnostic criteria [34]. Despite the low specificity of this neuro-imaging finding, The European Federation of Neurological Societies (EFNS) guidelines suggest that the detection of CST hyperintensities on T2-weighted, proton density, or FLAIR imaging can support a pre-existing (clinical) suspicion of motor neuron disease (e.g. ALS), as in our patients [42].

EMG studies confirmed evidence of lower motor neurons disease in most of the cases. CSF analysis was almost invariably abnormal: in this regard, we would like to underline the importance of OCB testing since this represents the most common (and sometimes the only) CSF abnormality. A

previous study reported by Dalmau et al. [5] suggested that Ma2-Ab paraneoplastic syndromes tend to respond poorly to immunotherapy, and partially (stabilization of symptoms) to tumor-removal. The series of cases reported in the literature that we present herein is in agreement with this finding. Conversely, 2/3 patients admitted to our center markedly improved following cancer treatment and immunotherapy, and 1 showed great improvement in motor function. This apparent discrepancy could be explained by the fact that all patients admitted in our Institution received aggressive (second-line) immunotherapy, with either cyclophosphamide and/or rituximab, whereas only 1/38 patients in the series reported by Dalmau et al. [5], and 1/7 in the present literature series, were treated with second-line therapies. Based on our patients and those of the literature, we speculate that a subset of around 10% of Ma2-Ab patients develops an immune-mediated attack to motor neurons, with anterograde degeneration of CST, and this could be a potentially treatable cause of MNS. This intriguing hypothesis needs to be verified in prospective clinical and pathological studies. The reason why only a minority of Ma2-Ab patients—and in general, a minority of patients with PNS—develop motor neuron involvement, is still unclear. We acknowledge that, in the majority of the patients of the present study, motor involvement manifested only after, or in association with, signs/symptoms that are known to be atypical for ALS diagnosis (namely, hypersomnia, hyperphagia, and sexual dysfunction). None of our patients presented with an isolated MNS that could be mistaken for ALS on clinical grounds. We, therefore, do not believe that routine Ma2-Ab testing should be performed in every patient presenting with ALS phenotype.

Although all patients had symptoms, signs, and neurophysiological evidence of neurodegenerative diseases such as ALS, primary lateral sclerosis (PLS), or progressive muscular atrophy (PMA), we have preferred the term MNS for patients with Ma2-Ab associated PNS. Because ALS has always been an invariably fatal disease and patients with Ma2-Ab-associated MNS have shown an improvement or at least stabilization in motor symptoms when treated with aggressive immunotherapy, we prefer to distinguish the diagnoses. The presence of detectable onconeural antibodies, OCBs, and cancer in the majority of patients with Ma2-Ab and MNS, together with the possibility of improvement after immunotherapy, suggest that the coexistence of MNS with paraneoplastic syndrome cannot be by chance alone but is driven by Ma2-Ab autoimmune response. In addition to its retrospective design and its small size, limitations of the present study include the incomplete description of the motor involvement in some of the cases reported in the literature, and the lack of genetic testing for ALS-related genes, although no patient admitted to our center demonstrated a positive family history for the disease.

We recognize also the fact that half of the patients in the present study developed a MNS in association with a "non-classical" PNS, and three of them had a negative cancer screening. Nevertheless, they should be considered "definite" PNS cases, since the neurological syndromes developed in association with a well-characterized Abs (Ma2-Abs) [4]. Using the Graus criteria, it is possible to include a very small number of false positive cases (approximately 4%) that will never develop cancer, possibly because the tumor was eliminated by the immune response [4]. Conversely, the possibility of "true" false positive cases (patients with a neurological syndrome unrelated to a PNS) is highly unlikely, since the recommended diagnostic approach require diagnostic confirmation using two independent techniques (immunohistochemistry and dot-blot analysis), as performed in our study.

In conclusion, motor neuron and CST involvement could complicate Ma2-Ab associated paraneoplastic syndromes and represent a treatable cause of MNS. Neurologists should be aware of this possibility and targeted interview regarding new-onset weakness, fasciculation, or bulbar symptoms should be routinely performed, especially in patients presenting initially with hypersomnia. Extensive tumor screening is recommended, since most of the cases harbor an underlying (usually testicular) tumor. Tumor-removal and immunotherapy could be effective in improving neurological syndromes and second-line treatments (with either cyclophosphamide, rituximab, or their combination) should be considered early if first-line treatments fail.

This disorder differs from ALS, which is an invariably fatal neurodegenerative disease, without the evidence of a paraneoplastic origin.

Acknowledgements We thank NeuroBioTec Hospices Civils de Lyon BRC (France, AC-2013-1867, NFS96-900) for banking sera and CSF samples. We gratefully acknowledge Philip Robinson for English language editing (Direction de la Recherche Clinique, Hospices civils de Lyon).

Author contributions Study concept and design: AV, JH. Acquisition of data: AV, BJ, AM, LT, EB, NS, FC, FD, and JH. Analysis and interpretation of data: AV, BJ, AM, LT, EB, NS, FC, FD, and JH. Drafting of the manuscript: AV, JH. Critical revision of the manuscript for important intellectual content: AV, BJ, AM, LT, EB, NS, FC, FD, and JH. Study supervision: Honnorat.

Funding This study is supported by research grants from ANR (ANR-14-CE15-0001-MECANO), FRM (Fondation pour la recherche médicale) DQ20170336751 and CSL Behring France.

Compliance with ethical standards

Data access, responsibility, and analysis The corresponding author had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Conflicts of interest Dr Vogrig reported receiving a fellowship grant from the European Academy of Neurology (EAN). No other disclosures were reported.

Ethical standards All procedures were performed in accordance with the institutional ethics committee and the Declaration of Helsinki.

References

1. Darnell RB, Posner JB (2003) Paraneoplastic syndromes involving the nervous system. N Engl J Med 349:1543–1554
2. Giometto B, Grisold W, Vitaliani R et al (2010) Paraneoplastic neurologic syndrome in the PNS Euronetwork database: a European study from 20 centers. Arch Neurol 67:330–335
3. Corcia P, Gordon PH, Camdessanche JP (2015) Is there a paraneoplastic ALS? Amyotroph Lateral Scler Frontotemporal Degener 16:252–257
4. Graus F, Delattre JY, Antoine JC et al (2004) Recommended diagnostic criteria for paraneoplastic neurological syndromes. J Neurol Neurosurg Psychiatry 75:1135–1140
5. Dalmau J, Graus F, Villarejo A et al (2004) Clinical analysis of anti-Ma2-associated encephalitis. Brain 127:1831–1844
6. Waragai M, Chiba A, Uchibori A, Fukushima T, Anno M, Tanaka K (2006) Anti-Ma2 associated paraneoplastic neurological syndrome presenting as encephalitis and progressive muscular atrophy. J Neurol Neurosurg Psychiatry 77:111–113
7. Hoffmann LA, Jarius S, Pellkofer HL et al (2008) Anti-Ma and anti-Ta associated paraneoplastic neurological syndromes: 22 newly diagnosed patients andreview of previous cases. J Neurol Neurosurg Psychiatry 79:767–773
8. Piccolo G, Tavazzi E, Jarius S et al (2011) Anti-Ma2/Ta antibodies in a woman with primary lateral sclerosis-like phenotype and Sjögren syndrome. Neurol Sci 32:915–917
9. Murphy SM, Khan U, Alifrangis C et al (2012) Anti Ma2-associated myeloradiculopathy: expanding the phenotype of anti-Ma2 associated paraneoplastic syndromes. J Neurol Neurosurg Psychiatry 83:232–233
10. Geevasinga N, Burrell JR, Hibbert M, Vucic S, Ng K (2014) C9ORF72 familial motor neuron disease—frontotemporal dementia associated with lung adenocarcinoma and anti-Ma2/Ta antibodies: a chance association? Eur J Neurol 21:e31–e33
11. Vogrig A, Ferrari S, Tinazzi M, Manganotti P, Vattemi G, Monaco S (2015) Anti-Ma-associated encephalomyeloradiculopathy in a patient with pleural mesothelioma. J Neurol Sci 350:105–106
12. Compta Y, Iranzo A, Santamaría J, Casamitjana R, Graus F (2007) REM Sleep behavior disorder and narcoleptic features in anti-Ma2-associated encephalitis. Sleep 30:767–769
13. Ney DE, Messersmith W, Behbakht K (2014) Anti-Ma2 paraneoplastic encephalitis in association with recurrent cervical cancer. J Clin Neurol 10:262–266
14. Matsumoto L, Yamamoto T, Higashihara M et al (2007) Severe hypokinesis caused by paraneoplastic anti-Ma2 encephalitis associated with bilateral intratubular germ-cell neoplasm of the testes. Mov Disord 22:728–731
15. Morelli-Zaher C, Varvat J, Duboeuf F, Antoine JC, Vergnon JM (2012) Non-small cell carcinoma presenting as limbic encephalitis. Place of endobronchial ultrasound in the diagnosis. Rev Mal Respir 29:719–722
16. Park MS, Bae JH, Jeong HB et al (2015) Anti-Ma2 antibody encephalitis manifesting as cognitive impairment and psychosis. J Neuropsychiatry Clin Neurosci 27:221–222
17. Szkandera J, Ploner F, Bauernhofer T et al (2010) Paraneoplastic limbic encephalitis in a patient with extragonadal choriocarcinoma-significance of onconeural antibodies. Onkologie 33:452–454
18. Edvardsson B (2011) Anti-Ma2-positive paraneoplastic brainstem encephalitis associated with prostatic adenocarcinoma. Neurol India 59:912–913
19. Bosemani T, Huisman T, Poretti A (2014) Anti-Ma2-associated paraneoplastic encephalitis in a male adolescent with mediastinal seminoma. Pediatr Neurol 50:433–434
20. García-Reitboeck P, Thompson G, Johns P, al Wahab Y, Omer S, Griffin C (2014) Upbeat nystagmus in anti-Ma2 encephalitis. Pract Neurol 14:36–38
21. Guan HZ, Huang Y, Zhong DR et al (2015) Anti-Ma2 paraneoplastic encephalitis associated with ileal lymphoma. Chin Med J (Engl) 128:1836–1837
22. Khammassi N, Balhouane I, Gargouri A, Gouider R, Cherif O (2012) Paraneoplastic neurological syndrome associated with anti-Ma2 antibodies. Rev Neurol Paris 168:192–193
23. Abdulkader MM, Yousef MM, Abdelhadi MK, Amr SS, Alabsi ES, al-Abbadi MA (2013) Microscopic dysgerminoma associated with anti-Ma2 paraneoplastic encephalitis in a patient with gonadal dysgenesis. Int J Gynecol Pathol 32:277–282
24. Biotti D, Viaccoz A, Olivier N et al (2012) Opsoclonus, limbic encephalitis, anti-Ma2 antibodies and gastric adenocarcinoma. Eur J Neurol 19:144–145
25. Ayrignac X, Castelnovo G, Landrault E et al (2008) Ma2 antibody and multiple mononeuropathies. Rev Neurol 164:608–611
26. Kerling F, Blümcke I, Stefan H (2008) Pitfalls in diagnosing limbic encephalitis—a case report. Acta Neurol Scand 118:339–342
27. Archer HA, Panopoulou A, Bhatt N, Edey AJ, Giffin NJ (2014) Mesothelioma and anti-Ma paraneoplastic syndrome; heterogeneity in immunogenic tumours increases. Pract Neurol 14:33–35
28. Kimura M, Onozawa M, Fujisaki A et al (2008) Anti-Ma2 paraneoplastic encephalitis associated with testicular germ cell tumor treated by carboplatin, etoposide and bleomycin. Int J Urol 15:942–943
29. Al-Thubaiti I, al-Hayek K, Binfalah M (2013) Anti-Ma-associated encephalitis due to dysgerminoma in a woman with Swyer syndrome. Neurology 80:1439–1440
30. Overeem S, Dalmau J, Bataller L et al (2004) Hypocretin-1 CSF levels in anti-Ma2 associated encephalitis. Neurology 62:138–140
31. Dauvilliers Y, Bauer J, Rigau V et al (2013) Hypothalamic immunopathology in anti-Ma-associated diencephalitis with narcolepsy-cataplexy. JAMA Neurol 70:1305–1310
32. Flanagan EP, McKeon A, Lennon VA et al (2011) Paraneoplastic isolated myelopathy: clinical course and neuroimaging clues. Neurology 76:2089–2095
33. Osborn B (2004) Salzman, et al. Diagnostic imaging brain, 1st edn. Amyrsis, Salt Lake City
34. Wingerchuk DM, Banwell B, Bennett JL et al (2015) International consensus diagnostic criteria for neuromyelitis optica spectrum disorders. Neurology 85:177–189
35. Kassubek J, Bretschneider V, Sperfeld AD (2005) Corticospinal tract MRI hyperintensity in X-linked Charcot–Marie–Tooth Disease. J Clin Neurosci 12:588–589
36. Uluc K, Baskan O, Yildirim KA et al (2008) Leukoencephalopathy with brain stem and spinal cord involvement and high lactate: a genetically proven case with distinct MRI findings. J Neurol Sci 273:118–122
37. Taft RJ, Vanderver A, Leventer RJ et al (2013) Mutations in DARS cause hypomyelination with brain stem and spinal cord involvement and leg spasticity. Am J Hum Genet 92:774–780
38. Loes DJ, Fatemi A, Melhem ER et al (2003) Analysis of MRI patterns aids prediction of progression in X-linked adrenoleukodystrophy. Neurology 61:369–374

39. Bajaj M, Mody S, Natarajan G (2014) Clinical and neuroimaging findings in neonatal herpes simplex virus infection. J Pediatr 165:404–407
40. Konagaya M, Iida M (1991) A case of HTLV-1 associated myelopathy with diffuse white matter lesion of the frontal lobe and continuous lesion of the pyramidal tract on cranial MRI. Rinsho Shinkeigaku 31:875–877
41. Tan MB, McAdory LE (2016) Capecitabine-induced leukoencephalopathy involving the bilateral corticospinal tracts. J Radiol Case Rep 10:1–10
42. Filippi M, Agosta F, Abrahams S et al (2010) EFNS guidelines on the use of neuroimaging in the management of motor neuron diseases. Eur J Neurol 17:526-e20